REMARKS/ARGUMENTS

THE INVENTION

This invention is based the discovery of unexpected synergy between an anti-VEGF and thymidilate synthase inhibitor when combined with 5,10, methylene tetrahydrofolate [5,10-CH_2FH_4] compared to leucovorin the purported equivalent co-factor to 5,10, methylene tetrahydrofolate.

STATUS OF THE CLAIMS

Claims 258- 278 are pending. Claim 258 has been amended to recite specific cancers.

No new matter has been introduced. Support for the amendments reciting colorectal cancer and breast cancer find support in original claim 268.

Claims 262-263 are withdrawn and applicants argue below for reconsideration.

Claims 268-278 were withdrawn and are now cancelled.

REJECTIONS

35 U.S.C. §112.

In the outstanding Office Action, the Examiner expressed concern over the claim scope and stated that the claims were only enabled for colorectal cancer and breast cancer. The claims have now been amended to recite those specific cancers. In view of the amendments, the applicants submit that the rejection under §112 has been overcome.

35 U.S.C. §103

The pending claims have been rejected as obvious over Hurwitz (2003), Carlsson (1997) and Anon (2003). A full copy of Anon (2003) is attached as **Exhibit 1**. Hurwitz discloses the use of leucovorin as a co-factor for F-FU in combination with Avastin, an anti-

VEGF antibody. Carlsson teaches that leucovorin is a prodrug that is metabolized into 5,10-CH_2FH_4. Carlsson further explains that 5,10-CH_2FH_4 forms stable complexes of TSFDuMP-folate resulting in the desired TS inhibition. TS inhibition chemotherapies involve a careful balancing by oncologists of therapeutic benefit and toxicity. Leucovorin and 5,10-CH_2FH_4 are used to render drugs like 5-FU more effective at tumor load reduction and safer to use. The conventional wisdom of the medical community is that the two co-factor drugs are virtually interchangeable. Carlsson clearly states on page 266, at column 2, that leucovorin is the preferred drug because of toxicity issues with the breakdown of 5,10-CH_2FH_4 into formaldehyde. On page 271, column 2, the authors discuss the relative advantages of leucovorin over 5,10-CH_2FH_4. However, the authors do not identify any clear advantage of one co-factor drug over the other. Anon (2003) teaches the use of capecitabine, a prodrug TS inhibitor (5-FU) combined with bevacizumab (Avastin) to treat breast cancer.

Applicants concede that the substitution of 5,10-CH_2FH_4 for leucovorin sets forth a proper *prima facie* case of obviousness. However, as the Examiner knows, a legally proper *prima facie* case of obviousness can be traversed by evidence of surprising and advantageous results. Applicants respectfully submit that the specification provides such evidence of unexpected and advantageous results for the combination of 5,10-CH_2FH_4, 5-FU and an anti-VEGF antibody, as compared to the combination of leucovorin, 5-FU and an anti-VEGF antibody. The data shows that there is a dramatic sensitization of the cancer cells to the combination therapy when 5,10-CH_2FH_4 is used rather than leucovorin.

Example 2 and Figures 7 and 8 describe the results of an experiment where nude mice were injected with HT-29 tumor cells and the tumor load measured under various experimental treatments. Among the treatments was a comparison between leucovorin and 5,10-CH_2FH_4 using combination therapy of an anti-VEGF antibody and F-FU.

The results on pages 53-54 illustrate a clear and surprising superiority for 5,10-CH_2FH_4 over leucovorin. The doubling time for tumor volume was reduced by more than a day, and the mean volume of tumor was reduced to 94 mm^3 from 140 mm^3 after 19 days. The results continued up until 25 days (Figure 7).

Such differences were not predictable or expected from the literature which generally describes 5,10-CH_2FH_4 and leucovorin as equivalents. The surprising benefits of combining 5,10-CH_2FH_4 with a TS inhibitor and an anti-VEGF antibody over leucovorin are particularly important from a clinical perspective. The small ratio (therapeutic split) between the dose providing therapeutic benefit and the dose causing toxicity for TS inhibitors make their use expensive and time intensive from the oncologist's perspective as they do what they can to minimize patient discomfort or death. The significant benefits of 5,10- CH_2FH_4 over leucovorin will mean that doses of TS inhibitors can be reduced without compromising benefit. Alternatively, an oncologist might elect to increase doses of TS inhibitors or use a more aggressive cycling of administration.

Beyond the surprising synergy of 5,10-CH_2FH_4 over leucovorin, applicants also discovered that 5,10-CH_2FH_4 provides 5-FU with a surprisingly greater safety profile. As seen in Example 4, mice treated with 5-FU and gemcitabine lost less weight when treated with 5,10-CH_2FH_4 than when treated with leucovorin. And as seen in Example 5, mice exhibited less 5-FU-induced lymphopenia (lymphocyte toxicity) when treated with 5,10-CH_2FH_4 than when treated with leucovorin.

As a final point, applicants would have the Examiner note that the pharmaceutical art of combination drug therapy is often unexplainable and unpredictable. On page 6 of the Office Action, the Examiner himself noted that "the art of developing and testing anticancer drugs, particularly for use in humans, is extremely unpredictable," and it was for this reason that the Examiner asserted that the present invention was not enabled for every type of cancer. This unpredictability is equally as true, if not more so, with regard to the art of combining drugs. For example, Figure 4 of the application illustrates the mean tumor volume for 5-FU, 5,10-CH_2FH_4 and oxaliplatin. The combination surprisingly resulted in no benefit in tumor reduction, despite that fact that 5-FU or oxaliplatin when used alone has been found to be effective! For this reason, the Examiner's assertion that there would have been a reasonable expectation of success for the combination of the present invention in view of the cited art (with respect to leucovorin) is not sustainable, and the Examiner is respectfully requested to rescind his rejection on these grounds.

Reconsideration Of The Withdrawal Of Claims 262-263 Reciting Capecitabine

The Examiner has maintained the restriction requirement effectively dividing the claims between TS inhibitors (such as 5-FU) and where the TS inhibitor is a prodrug of the commonly used 5-FU. The Examiner's concern about a second species having a third component is not clear. There is really no valid legal reason to divide the claims between drugs when the class is being claimed and already examined. In view of this, reconsideration of the withdrawal of claims 262-263 is requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Capecitabine/Bevacizumab Compared to Capecitabine Alone in Pretreated Metastatic Breast Cancer: Results of a Phase III Study

Introduction

• Angiogenesis, the process of new blood vessel formation, is a crucial step in tumor growth and metastasis.[1] Vascular endothelial growth factor (VEGF) is a well characterized angiogenic factor, the receptors for which are found predominantly on endothelial cells. High VEGF expression by tumors is an indicator for poor prognosis and survival.[2,3] Thus VEGF has emerged as a target for anticancer therapy.

• Bevacizumab (Avastin™) is a humanized anti-VEGF monoclonal antibody that has known antitumor activity in previously treated metastatic breast cancer (MBC).[4] Cobleigh and colleagues conducted a phase II study of bevacizumab in 75 women with previously treated MBC.[4] Patients received either 3, 10, or 20 mg/kg bevacizumab intravenously (I.V.) every 2 weeks with a median treatment duration of 10 weeks. Seven patients had an objective response for an overall response rate (RR) of 9.3%. Twelve patients (16%) achieved stable disease and the median survival time was 10.2 months.

• The pharmacokinetics of capecitabine mimic those of continuous infusion 5-fluorouracil (5-FU). It is administered orally, usually at a dose of 1000-1250 mg/m^2 by mouth (p.o.) twice a day (b.i.d.) on days 1-14 every 3 weeks. Phase II studies of capecitabine monotherapy have shown efficacy as treatment for patients previously treated with anthracyclines and taxanes, with RRs ranging from 20%-36% and a tolerable toxicity profile, especially with respect to myelosuppression, which was minimal.[5-8] A randomized phase II study conducted by O'Shaughnessy and colleagues comparing capecitabine to CMF (cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-FU 600 mg/m^2) as first-line therapy in MBC patients ≥ 55 years of age showed that the RR (30% vs. 16%), median time to progression (4.1 months vs. 3.0 months), and median overall survival (19.6 months vs. 17.2 months) favored patients treated with capecitabine over I.V. CMF.[9]

• Based on the encouraging results of the phase II study of bevacizumab monotherapy and the proven activity of capecitabine in MBC, a phase III study of this combination was initiated. Miller and colleagues conducted the phase III study of capecitabine with or without bevacizumab in MBC patients who had been previously treated with an anthracycline and a taxane. The main objective of this study was to determine and compare time to disease progression as well as overall efficacy and safety in patients receiving capecitabine and capecitabine/bevacizumab. The results of this study were recently presented at the 25th Annual San Antonio Breast Cancer Symposium.[10]

Capecitabine in Combination with Bevacizumab

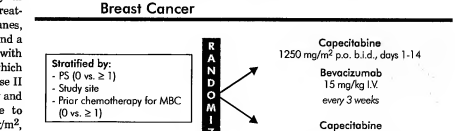
This study included MBC patients with progressive disease who had received 1 or 2 prior chemotherapy regimens for metastatic disease and who had been previously treated with an anthracycline and a taxane. Patients whose disease recurred within 12 months of completing an anthracycline and taxane-containing adjuvant regimen were also eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and should not have received antitumor therapy within 21 days prior to study entry. Patients with central nervous system metastases or significant proteinuria (> 500 mg/24 hours) were excluded from this study.

Patients were stratified by PS (0 vs. ≥ 1) and prior chemotherapy for MBC (0 vs. ≥ 1) and were randomized to treatment with capecitabine 1250 mg/m^2 p.o. b.i.d. on days 1-14 every 3 weeks or capecitabine 1250 mg/m^2 plus bevacizumab 15 mg/kg I.V. every 3 weeks (Figure 1).

Results

A total of 462 patients were enrolled on this study. The median age was 52 years (range, 30-77 years) and 50 years (range, 29-78 years) in the capecitabine and capecitabine plus bevacizumab arms, respectively. Approximately half of the patients in each arm were estrogen receptor-positive and a quarter of patients in each arm were HER2-posi-

Figure 1. Treatment Schema for Capecitabine Versus Capecitabine/Bevacizumab in Metastatic Breast Cancer



Abbreviations: MBC = metastatic breast cancer; PS = performance status

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Exhibit 1

Table 1. Efficacy of Capecitabine Versus Capecitabine/Bevacizumab

Response Rate	Capecitabine (n = 230)	Capecitabine/Bevacizumab (n = 232)	P Value
Response Rate (Investigator Assessed)	19.1%	30.2%	0.006
Response Rate (IRF Assessed)	9.1%	19.8%	0.001
Duration of Response (Investigator Assessed)	6.7 months	4.96 months	NS
Duration of Response (IRF Assessed)	7.56 months	4.96 months	NS
Progression-Free Survival	4.17 months	4.86 months	NS

Abbreviations: IRF = independent review facility; NS = not significant

tive. Approximately 80% of patients had received ≥ 1 prior chemotherapy regimen for metastatic disease and the viscera was found to be the primary site of metastatic disease in approximately 75% of patients on each arm.

The overall RR as assessed by the investigators and then reviewed by an independent review facility (IRF) was significantly higher in patients treated with capecitabine/bevacizumab compared with capecitabine alone. The investigator-assessed RR was higher in the capecitabine/bevacizumab arm at 30.2% versus 19.1% ($P = 0.006$) compared with capecitabine alone. Similarly, the addition of bevacizumab doubled the RR as assessed by the IRF (19.8% vs. 9.1%; $P = 0.001$). However, addition of bevacizumab did not improve the duration of response, which was longer in patients with capecitabine alone (7.56 months vs. 4.96 months as assessed by the IRF and 6.7 months vs. 4.96 months as assessed by the investigators, in the capecitabine arm vs. the capecitabine/bevacizumab arm, respectively; Table 1).

Median progression-free survival (PFS) was similar in the 2 arms at 4.17 months and 4.86 months in the capecitabine arm versus the capecitabine/bevacizumab arm, respectively (Table 1).

The major grade 3 capecitabine-related toxicity was hand-foot syndrome, which was experienced by approximately a quarter of the patients on both treatment arms. Grade 3 diarrhea was seen in a similar number of patients in both arms. The most frequent bevacizumab-associated toxicities were minor bleeding events (28.8% vs. 11.2% for capecitabine alone) and proteinuria (22.3% vs. 7.4% for capecitabine alone). Grade 3 hypertension was also more common in patients treated with bevacizumab at 17.9% compared to 0.5% of patients treated with capecitabine alone. There appeared to be no significant increase in thromboembolic events with the addition of bevacizumab (Table 2).

Table 2. Toxicity of Capecitabine Versus Capecitabine/Bevacizumab

	Capecitabine (n = 215)	Capecitabine Plus Bevacizumab (n = 229)
Capecitabine-Associated Toxicity (Grade 3)		
Hand-foot syndrome	24.2%	27.5%
Diarrhea	10.7%	11.8%
Bevacizumab-Associated Toxicity		
Hypertension (grade 3)	0.5%	17.9%
Thromboembolic events	5.6%	7.4%
Bleeding events	11.2%	28.8%
Grade ≥ 3	1.4%	0.4%
Proteinuria	7.4%	22.3%
Other Grade 3/4 Toxicities < 10%		
Congestive heart failure	0.9%	3.1%
Dyspnea	5.1%	7.4%
Vomiting	4.2%	2.6%
Stomatitis	0.5%	1.7%

Conclusion

This phase III study demonstrated that the addition of bevacizumab to capecitabine improved RR in anthracycline and taxane-pretreated MBC patients. However, there was no improvement in either response duration or PFS with capecitabine/bevacizumab compared to capecitabine alone.

Further studies of bevacizumab in previously untreated patients are ongoing, including ECOG 2100 (for details see pages 421-422), which is comparing paclitaxel with or without bevacizumab in patients previously untreated with chemotherapy for their metastatic disease.

References

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